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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHEINBERG, MONIKA B	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,216	BROWN ET AL.	
	Examiner	Art Unit	
	Monika B Sheinberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10 and 20-25* is/are pending in the application.

4a) Of the above claim(s) *25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10 and 20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *10 and 20-25* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) ~~Paper No(s)/Mail Date~~ 1 sheet MBS 4/28/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*.

DETAILED ACTION

Response to Amendment filed: December 9, 2003

1. The cancellation of claims 8 and 11-19, and the addition of new claims 20-25 are acknowledged.

2. It is to be noted that claim 25 is drawn to a nonelected invention (SEQ ID NO: 1). However, Examiner has assumed the reference to SEQ ID NO: 1 and not SEQ ID NO: 7 is a typographical error in order to expedite prosecution. SEQ ID NO: 1 has not and will not be searched. The elected sequence of the instant invention is SEQ ID NO: 7. Correction is requested.

3. In regards to the continued traversal of the restriction requirement mailed: 15 May 2003, the restriction has been made final in the previous action mailed: 09 September 2003. With respect to the sequence restriction requirement, Applicants further assert that it would not be a serious burden to search ten sequences. This is not found persuasive because SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 are completely distinct sequences. A prior art search of SEQ ID NO: 7 would not necessarily be relevant to the art of the other sequences. In addition, the size of sequence databases has increased over the past years significantly, thereby presenting a significant burden to search multiple sequences in the sequence databases. Further, the claims are directed to a single sequence of the ten to be correlated to the claimed nucleic acid molecule. The requirement is still deemed proper and is therefore maintained as FINAL.

4. Applicants' arguments, filed: 09 December 2003, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

5. Claims 10 and 20-25 are pending.

6. Claims 10 and 20-25 are hereby examined as directed to SEQ ID NO: 7.

NEW GROUNDS FOR REJECTION

AS NECESSITATED BY AMENDMENT

Claim Rejections - 35 USC § 101 and 112

7. The pending claims have been reviewed in light of the Utility Examination Guidelines and Guidelines for Examination of Patent Applications under 35 U.S.C. 112, first paragraph, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1092-1111, Friday, January 5, 2001.

The examiner is using the following definitions in evaluating the claims for utility.

"Specific" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention.

"Substantial" - A utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

"Credible" - Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record that is probative of the applicant's assertions. That is, the assertion is an inherently unbelievable undertaking or involves implausible scientific principles.

"Well-established" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

35 U.S.C. § 101

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

8. Claims 10 and 20-25 are rejected as necessitated by amendment under 35 U.S.C. § 101 because the claimed invention lacks patentable utility due to its not being supported by a substantial utility.

The rejection of claim 10 is maintained for reasons of record and newly applied to the amendment of claim 10 and the newly added claims 20-25 as necessitated by amendment.

The claims are drawn to an isolated nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO: 7. The specification generally teaches identification of sequences (such

as SEQ ID NO: 7) by subtractive library hybridization techniques (example 2, p. 207). The specification teaches that SEQ ID NO: 7 was identified from library CMz031 (Lib148) (Table A and p. 170). The specification teaches that the library-designated CMz031 was CDNA prepared from maize pollen tissue at a particular developmental stage (V10+, p. 170). The specification asserts that SEQ ID NO: 7 encodes a "maize or soybean copalyl diphosphate synthase enzyme or fragment thereof" (p. 16, lines 15-17) thereby be useful to identify and obtain homologues in both maize and non-maize plants (p. 42-43, line 20 to line 4 respectively).

The asserted specific utilities are based upon homology/identity to experimentally known sequences of the cDNA; kaurene synthase A (gi576885, 03-Aug-1995; Table A and p. 42).

It is noted that applicant(s) have listed this sequence which is known in the prior art and which has a high percentage sequence similarity (95%, table A) to a claimed sequence, SEQ ID NO: 7. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed nucleotide and the indicated similar nucleotides of known function and therefore lacks support regarding utility and/or enablement. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over polypeptides of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Gerhold *et al.*[*BioEssays*, vol. 18, n. 12, pp. 973-981(1996)]; Wells *et al.*[*J. Leukocyte Biol.*, vol. 61, n. 5, pp. 545-550 (1997)]; and Russell *et al.*[*J. Molecular Biol.*, vol. 244, pp. 332-350 (1994)].

Further, it is unpredictable if SEQ ID NO: 7 will successfully encode a functional enzyme in that it is not indicated to be a full-length open reading frame. The elected sequence is not disclosed as a full-length open reading frame of the synthase that it is predicted to encode. As per the specification the claimed sequences are "randomly selected clones [that] comprise insets that **can** represent a copy of **up to** the full length of a mRNA transcript" (emphasis added). In addition, it unclear as what function is asserted since SEQ ID NO: 7 after review of the links

to database entries is associated the function of kaurene synthase A (copalyl diphosphate synthase). The potential specific utility of the partial enzyme is determined by sequence alignment and not by experimentation, no actual full length enzyme with a defined functionality or biological activity is disclosed, and the specification does not disclose whether the partial sequence of SEQ ID NO: 7 represents an active fragment or what activity it has, thus there is no certainty in having a useful isolated product with which to perform the potential assays to study/modify the gibberellin pathway. The specification asserts that the nucleic acid would encode polypeptide compounds, proteins, that may be useful in a variety functional/biological activities based on a correspondence of similarity to a known protein.

In addition, the nucleic acid is not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. For example, the nucleic acid is not experimentally characterized in any fashion, but partially characterized by predictions based on homology analyses to public database entries. The research contemplated by applicant(s) to characterize the nucleic acid or potential enzyme products, especially their biological activities, does not constitute a specific and substantial utility. Identifying and studying the properties of a nucleic acid, its potential enzyme product or the mechanisms in which the enzyme is involved does not define a "real world" context or use. Thus the insubstantial utility of the provided sequence of record constitutes carrying out further research to identify or reasonably confirm the utility of the provided sequence, SEQ ID NO: 7.

9. The following is a quotation of the **first** paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 10 and 20-25 are rejected as necessitated by amendment under 35 U.S.C. 112, first paragraph, Specifically, since the claimed invention is not supported by a specific, substantial, and credible utility or a well-established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Response to Arguments: 35 U.S.C. 101/112

11. The Applicants' arguments have been fully considered and have not been found persuasive.

The current USPTO utility guidelines state (*emphasis added*):

"Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes chromosome markers, or forensic or diagnostic markers. Therefore the credibility of such an assertion would not be questioned, although such a use might fail the- specific and substantial tests (see below).

"Specific Utility" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - A utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. *Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.*
B. *A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. ' 10 1.)*
C. *A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility."*
D. *A method of making a material that itself has no specific, substantial, and credible utility. '*
E. *A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.*

Note that "throw away" utilities do not meet the tests for a specific or substantial utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. ' 101. This analysis should, or course, be tempered by consideration of the context and nature of the invention. For example, it a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial asserted utility would be considered to be met.

A "Well established utility" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. 'Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this is the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paper weight; any carbon containing molecule would have a "well established utility" as a fuel since it can be burned; any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.

See also the MPEP at 2107 - 2107.02.

12. On page 9, 2nd paragraph; and page 10, 3rd paragraph of the response: Applicants assert that the 'Examiner has not provided any support for the proposition that the claimed nucleic acid molecules would not work for the recited utilities; or that one skilled in the art would doubt that the claimed nucleic acid molecules would work for the utilities disclosed. This argument has been thoroughly reviewed but is not found to be persuasive because the potential specific utility of the enzyme is determined by sequence characteristic prediction and not by experimentation; no actual enzyme with a defined functionality or biological activity is disclosed thus no certainty in having a useful isolated product with which to perform the potential assays to study/modify the gibberellin pathway. The specification asserts that the nucleic acid would encode polypeptide compounds, proteins, that may be useful in a variety functional/biological activities based on a correspondence of similarity to a known protein with less than 100% homology. A percentage sequence similarity of less than 100 % homology and fragments including 100% homology, is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter, would be the same as that of such a similar known polypeptide absent factual evidence. The claim language reads on a fragment of i.e. 20 bp with 95% homology to SEQ ID NO: 7; therefore only 19 bp need be identical. The sequences encompassed by the claims need not be 95% identical to the overall sequence of SEQ ID NO: 7, but 95% to only a portion whereupon it is unpredictable if the homology will be the same with the full length protein of which SEQ ID NO: 7 only encodes a part of; in addition to whether it would retain any of the ability for the cyclization of gernaylgeranyl diphosphate to copalyl diphosphate. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. Any variation in amino acid sequence results in a new

and independent sequence that does not necessarily reliably result in similar or identical biological activities as result, for example, from altered folding patterns. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. In the instant case, since the function/activity of SEQ ID NO: 7 is only based upon structure similarity of less than 100% to the maize enzyme, the claimed sequence structure/function relation is unpredictable, thus unreliable, and therefore lacks support regarding utility and enablement. For further clarification of the lack predictability, the state of the art teaches that sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide. Bork [Genome Research, 10: 398-400 (2000)] teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Van de Loo et al. [PNAS 92; 6743-6747 (1995)] teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* were found to be hydroxylases once tested for activity. Seffernick et al. [J. Baceriol. 183 (8); 2405-2410 (2001)] teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. [Science 282: 1315-1317 (1998)] teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydroxylase and as few as six amino acid substitutions can transform a hydroxylase to a desaturases. Therefore, as stated above, any variation in amino acid sequence is largely unpredictable and results in a new and independent sequence that does not necessarily reliably result in a peptide having similar or identical biological activities when the biological activity of the peptide is known; and more specifically in the instant case, when SEQ ID NO: 7 is less than 100% homologous to a known maize enzyme and it is unknown which region of SEQ ID NO: 7 are critical to its function for the cyclization of geranylgeranyl diphosphate to copalyl diphosphate.

13. On page 9, 3rd paragraph: Applicants point to Venter et al and Woese et al for support of sequence similarity being routinely used by those of ordinary skill in the art as a valuable predictor of function. The instant argument has been fully reviewed but is not found persuasive because the instant invention fails teach which regions of the claimed nucleic acid are essential to the bioactivity of SEQ ID NO: 7 thus rendering the nucleic acid either functional, non-

functional, or comprising a different function all together. In addition applicants are pointed to the state of the art post-filing date, teaches that sequence comparison alone should not be used to determine a protein's function and that small nucleic or amino acid changes can drastically change the function of the resulting polypeptide. [See section # 12 above].

14. On page 9, 4th paragraph: Applicants assert that other to the utility of the cyclization of geranlygeranyl diphosphate to copalyl diphosphate, the specification described multiple other utilities such as "isolating a variety of agronomically significant genes, acquiring molecular markers, promoters, cis-regulatory elements, identifying polymorphisms, and probes for assisting in the isolation of full-length cDNAs or genes, gene mapping, isolation of homologous sequences, and detection of gene expression." This argument has been thoroughly reviewed but not found persuasive because the specification has not taught the difference between a agronomic gene and non-agronomic genes; which molecular markers can be acquired and used as molecular markers; what the promoters or regulatory elements are for; what effect an identified polymorphism will have. In regards to the probes, the specification summarizes modern biotechnology generally but never connects the specifically elected sequence to any specific, substantial or well-established utility (aside from the predicted structure/function relationship that is demonstrated above to lack predictability and enablement). This wishlist desire for a utility for the claimed sequences falls short of a readily available utility. These are non-specific uses that are applicable to nucleic acid(s) in general and not particular or specific to the nucleic acids being claimed.

15. On page 10, 1st paragraph: Applicants further assert that the claimed nucleic acids can be used to identify elements related to the gibberellin pathway and to copalyl diphosphate synthase thereby satisfying at least one objective, utility. This argument has been fully reviewed but not found persuasive because the specification does not teach or suggest what elements and their associated function may be identified, and how these elements are involved in or associated to the gibberellin pathway or copalyl diphosphate synthase.

16. On page 10, 2nd paragraph: Applicants asserts that many of the described uses for the claimed nucleic acids are directly analogous to a microscope,

> An important utility of a microscope resides in its use to identify and characterized the structure of biological tissues in a sample, cell, or organism. Significantly, the utility of the microscope [...] is not compromised by its use as a tool in this manner.

This argument was thoroughly reviewed but not found persuasive because the nucleic acid of the present invention is not analogous to a microscope. A microscope has a specific and substantial utility of magnifying images to allow the visualization of items too small to be seen by the unaided eye. This utility is specific for a microscope and is based on the physical structure of the lenses and mirrors present within the microscope. Applicants are effectively arguing that a nucleic acid and microscope are analogous because they can be used as a research tool. However, the claimed nuclei acid can only be used to detect sequences that themselves have no specific and substantial utility. This is analogous to the disclosure of a microscope containing a slide which contains an unknown smear of matter and providing claims to the unknown smear of matter.

17. On page 10, 3rd paragraph to page 11, 1st paragraph: Applicants assert that there is "no requirement for exclusive utility" with respect to other molecules also being used for the same purpose as the claimed nucleic acids; "such an argument would imply that a new golf club has no legal utility because other golf clubs can be used for the same purpose, *i.e.* hitting golf balls." Thus Applicants assert the claimed nucleic acid molecules will identify a unique subset of related sequences while the golf club is uniquely designed to hit a ball in a manner that is distinct from other golf clubs. The argument is not persuasive because in the golf club case - a golf club has a specific and substantial utility and therefore an improved golf club for instance, would as well. This utility is directly dependent upon the structure of the golf club and the materials of which it is composed. In the instant case, no specific or substantial utility has been established for the claimed nucleic acid. A golf club is not structurally or functionally analogous to the nucleic acid of the present invention. Thus to be able to hit a golf ball in an effective and controlled manner because of the structure and composition of the club is a real world context of use, and is immediately apparent with no further experimentation needed to determine its use, whereas the

unique combination of the nucleotides within a nucleic acid molecule determines its specific function or activities; however in the instant case, further experimentation is required to determine its function. The asserted utilities for the present invention do not take advantage of the particular combination of nucleic acids in the present invention but rather rely on properties common to all nucleic acids. The utility is therefore considered non-specific.

Claim Rejections - 35 USC § 112

18. The following is a quotation of the **first** paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 20-25 are rejected as necessitated by amendment under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

20. In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described. They are:

> *Nature of the invention,*
> *State of the prior art,*
> *Predictability or lack thereof in the art,*
> *Amount of direction or guidance present,*
> *Presence or absence of working examples,*
> *Breadth of the claims,*
> *Quantity of experimentation needed, and*
> *Level of the skill in the art.*

The Nature of the Invention and the Breadth of the claims

21. The nature of the invention is the isolated nucleic acid comprising SEQ ID NO: 7, fragments thereof, and its complements that encode a maize copalyl diphosphate synthase enzyme (kaurene synthase A) or fragment thereof. The breadth of the claims is very broad and encompasses mutants, variants, or homologs of SEQ IDNO: 7 from any source and any

magnitude and/or content including those that may or may not encode a functional enzyme of the same or different activity of the cyclization of geranylgeranyl diphosphate synthase to copalyl diphosphate.

The state of the Prior Art and the Predictability or Lack Thereof in the Art

22. The prior art does not teach what the specification fails to teach in regards to how the skilled artisan can cyclize geranylgeranyl diphosphate synthase to copalyl diphosphate with the claimed nucleic acid fragments or encoded protein fragments, nor which portions of the enzyme is required to maintain the function for the cyclization of geranylgeranyl diphosphate synthase to copalyl diphosphate as a whole or partial enzyme. The specification fails to teach or suggest which specific amino acids can be altered by the skilled artisan without altering or destroying the function of copalyl diphosphate synthase for the cyclization of geranylgeranyl diphosphate synthase to copalyl diphosphate. Each variation results in a new and independent sequence that does not reliably result in similar or identical biological activities of the peptide in its entirety. The sequences encompassed by the claims are of any magnitude and/or content that comprise at least the specified region of SEQ ID NO: 7, and thus include flanking regions which are inclusive of mutations of the sequence that can alter the encoded protein's folding pattern. The state of the art teaches that sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide. It is known for proteins, for example, that even a single amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. Any variation in amino acid sequence results in a new and independent sequence that does not necessarily reliably result in similar or identical biological activities as the as result, for example, from altered folding patterns. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. In the instant case, the functional activity of the claimed sequence homologies and sequences containing only fragments of the entire sequence SEQ ID NO: 7, is unpredictable, thus unreliable, in maintaining the same bioactivity of the entire SEQ ID NO: 7, the claimed fragment, variant nucleic acid, its encoded enzyme and fragment thereof, and therefore lacks support regarding enablement. For further clarification of the lack predictability, the state of the art teaches that sequence comparison alone should not be used to

determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide. Bork [Genome Research, 10: 398-400 (2000)] teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Van de Loo et al. [PNAS 92; 6743-6747 (1995)] teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* were found to be hydroxylases once tested for activity. Seffernick et al. [J. Baceriol. 183 (8); 2405-2410 (2001)] teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. [Science 282: 1315-1317 (1998)] teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydroxylase and as few as six amino acid substitutions can transform a hydroxylase to a desaturases. Thus level of unpredictability is high in the art.

The Amount of Direction or Guidance Present and the Presence or Absence of Working Examples

23. The specification fails to provide guidance to the skilled artisan in how to make a fragment of the as encoded by a whole or partial sequence of SEQ ID NO: 7 that has the desired bioactivity. The specification does not provide any information for the activity or functional areas of the enzyme. Due to the specification failing to give the active regions or discuss what critical amino acids for this protein are, it is unpredictable as to which nucleotides can be altered to result in an active fragment with copalyl diphosphate synthase activity. Ideally, the use of examples in a given specification typically serve to demonstrate at least the critical limitations and/or requirements in order to make/use an invention. However, the examples are directed to the identification of sequences (such as SEQ ID NO: 7) by subtractive library hybridization techniques and not specific to the claimed sequences (partial or whole) that could encode a function enzyme. It is also unknown if SEQ ID NO: 7 itself encodes a functional fragment of the copalyl diphosphate synthase.

Quantity or Experimentation needed and Level of the Skill in the Art

24. The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which portions of SEQ ID NO: 7 and the critical active regions of the synthase that are critical to its bioactivity and then determine if portions containing such regions would maintain the same bioactivity of cyclization as the nucleic sequence that would encode the full peptide. One of skill in the art would then have to perform undue experimentation to determine which mutations or alterations (including magnitude and content) would result in a the claimed nucleic acids maintaining the same bioactivity as the entirety of the synthase. Due to the level of skill in the art being high and the unpredictability in the art being even higher, each embodiment of the invention is required to be individually assessed for functional activity. Such analysis is replete with unpredictable trial and error analysis and is considered undue. Thus, the specification fails to provide sufficient enablement for how to make or use the broadly claimed variant peptides. As a result necessitating one of skill to perform an exhaustive research and experimentation determine how to make or use the instantly claimed peptides.

25. Claims 10 and 20-25 are rejected as necessitated by amendment under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses SEQ ID NO: 7, asserted to encode a copalyl diphosphate synthase. The full-length exact sequence of SEQ ID NO: 7 per se, meets the written description provisions of 35 USC 112, first paragraph. However, the claims are directed to encompass gene sequences of any magnitude and/or content comprising SEQ ID NO: 7 or of SEQ ID NO: 7; a genus that is extremely large while that which is disclosed is a single sequence, SEQ ID NO: 7 in the Sequence Listing which is not representative of this large genus. For example, due to the "comprising" claim language of claim 10, claim 10 encompasses sequences of any magnitude and/or content comprising SEQ ID NO: 7. These sequences correspond to sequences from other species, mutated fragment sequences, allelic variants, splice variants, and so forth, including genomic sequences. None of these additional sequences meet the written description provision

of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim. This is a rejection based on a lack of WRITTEN DESCRIPTION.

Claims 20 and 21 require the isolated nucleic acid to encode a maize copalyl diphosphate synthase enzyme or fragment thereof, however the specification does not disclose the content of the sequence that differentiates between a the instant maize enzyme and a non-maize enzyme; what determines a fragment to specifically be of a maize copalyl diphosphate synthase sequence versus a non- maize copalyl diphosphate synthase. In addition, full length cDNA and genes would hybridize to these claimed nucleic acids, thus the claims reads on undisclosed, undescribed DNA molecules. While the fragment can be used to pull out the full length cDNA, this describes how to find the gene or the cDNA and does not describe the DNA molecule itself.

Claims 22-25 recite substantially purified nucleic acid molecules having between 100% and 90% sequence identity to SEQ NO: 7 or its complement (claim 22); a substantially purified nucleic acid having between 100% and 95% sequence identity with SEQ ID NO: 7 or its complement (claim 23); a substantially purified nucleic acid having between 100% and 98% sequence identity with SEQ ID NO: 7 or its complement (claim 24); and a substantially purified nucleic acid having between 100% and 99% sequence identity with SEQ ID NO: 7 or its complement (claim 25). The specification, however, does not disclose the content of this polymorphic region, thus claiming a function without structure. These claims read on a very broad and highly variable genus of nucleic acid molecules which includes variants, homologs, and mutants of SEQ ID NO: 7, with either retained or altered function.

Beyond providing the sequence data for SEQ ID NO: 7, the specification provides no teaching or guidance which correlates the sequence of SEQ ID NO: 7 to its function, which amino acids in the protein encoded by SEQ ID NO: 7 are critical to its function, or how to modify SEQ ID NO: 7 to obtain any specific homolog, mutant, or variant. It is not clear which positions with SEQ ID NO: 7 can be substituted or altered without resulting in a loss of the function of SEQ ID NO: 7. Therefore, the skilled artisan would be unable to determine whether or not a DNA molecule is functionally equivalent to SEQ ID NO: 7. The claims provide for a large genus of nucleic acids that include undisclosed genes, partial genomic sequences, mutants,

variants, and homologs of SEQ ID NO: 7, however the single disclosed structural feature of SEQ ID NO: 7 does not provide for a substantial portion of the claimed genus.

While one of skill in the art could argue that the claimed genus of polynucleotides is adequately described since one can isolate these polynucleotides by sequence comparison using the polypeptide/polynucleotide structures disclosed in the instant application or the prior art, the state of the art teaches that sequence comparison alone should not be used to determine a protein's function and that small amino acid changes can drastically change the function of a polypeptide. Bork [Genome Research, 10: 398-400 (2000)] teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Van de Loo et al. [PNAS 92; 6743-6747 (1995)] teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* were found to be hydroxylases once tested for activity. Seffernick et al. [J. Baceriol. 183 (8); 2405-2410 (2001)] teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. [Science 282: 1315-1317 (1998)] teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydroxylase and as few as six amino acid substitutions can transform a hydroxylase to a desaturases. The genus of polynucleotides comprised by the claim is a large variable genus, which can potentially encode proteins of diverse functions. The specification only discloses a single species of the genus, i.e. the polynucleotide of SEQ ID NO: 7, which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116.)

With the exception of a substantially purified nucleic acid molecule consisting of the sequence of SEQ ID NO: 7, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, regardless of the complexity or simplicity of the method of

isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In *Fiddes v. Baird*, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997);
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> *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Accordingly, the specification does not provide a written description of the invention of claims 10 and 20-25. This is a rejection based on a lack of WRITTEN DESCRIPTION.

Response to Arguments

26. On page 12, last paragraph: Applicant asserts that "it is not required that every aspect of those nucleic acid molecules (e.g., an open reading frame) be disclosed". This argument has been thoroughly reviewed but is not found to be persuasive because the specification does not reflect possession of mutants, variants, or homologs of SEQ IDNO: 7 from any source by merely disclosing the sequence of SEQ ID NO: 7, let alone those that encode a bioactive fragment. For example, isolation of SEQ ID NO: 7 does not reflect possession of mutants or variants of SEQ ID NO: 7, nor possession of nucleic acids of any magnitude and/or content. The sequences

encompassed by the claims are of any magnitude and/or content that comprise SEQ ID NO: 7 or at least the specified region of SEQ ID NO: 7: as seen in claim 22, for example, "wherein said nucleic acid molecule *comprises* a nucleic acid sequence that shares between 100% and 90% sequence identity with SEQ ID NO: 7." The claims remain encompassing sequences that are not described by the specification.

27. On page 13, 2nd paragraph: Applicants assert that the claims define "structural features commonly possessed by members of the genus that distinguishes them from others" however has not indicated how or where in the claims or the specification this is disclosed. If the bioactivity of the sequence or encoded peptide is intended, then as stated above, the specification fails to teach what structural features are critical to SEQ ID NO: 7 and its bioactivity.

28. On page 13, 3rd paragraph: Applications further assert that "[t]he fact that the nucleic acid molecules may comprise additional sequences or variations is beside the point. Such modifications are readily envisioned by one of ordinary skill in the art and disclosed through the present specification". This argument has been thoroughly reviewed but is not found to be persuasive because the specification does not teach how to modify SEQ ID NO: 7 or which modifications can be made in order to retain the same or different functional capabilities of the desired enzyme. Therefore an ordinary artisan could not readily envision which can and cannot be altered, inserted, deleted etc. [See also the lack of predictability in section number 25 (6th paragraph) above].

29. Therefore, the arguments are non-persuasive to overcome the rejection based on the lack of written description.

30. The following is a quotation of the **second** paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

31. Claims 22-25 are rejected as necessitated by amendment under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 are vague and indefinite due to the lack of clarity of the phrase "comprises a nucleic acid sequence that shares between 100% and 90% sequence identity with SEQ ID NO: 7." It is unclear as to which nucleic acid sequence of the elected sequence is required have 90%-100% identity and be comprised within the claimed isolated sequence. Currently, the claim reads on any sequence that contains at least 2 contiguous nucleotides of SEQ ID NO: 7. Thus it is unclear what is intended by the applicants to meet the limitations of the claim due to metes and bounds of the parameters that define a nucleic acid sequence of SEQ ID NO: 7.

Claim Rejections - 35 USC § 102

32. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

33. Claims 20-25 are rejected as necessitated by amendment under 35 U.S.C. 102(b) as being anticipated by GenBank accession number L37750 (gi 576885; 03-Aug-1995).

As per Table A of the specification, the GenBank accession number L37750 (gi 576885; 03-Aug-1995) has 95% identity to SEQ ID NO: 7 (claim 22). Thus the sequence also shares between 90% and 100% identity with SEQ ID NO: 7 (claim 21). In addition, the sequence encodes a kaurene synthase A (copalyl diphosphate synthase). With the high sequence homology, the sequence would hybridize to a sequence of SEQ ID NO: 7 and encode a copalyl diphosphate enzyme as required by claims 20 and 21. Due to the claims 22-25 requiring only that a nucleic acid sequence share a percent identity with SEQ ID NO: 7, as few as 2 bp of the instant accession number that align 100% anticipate the claimed nucleic acids.

34. Claims 20-25 are rejected under 35 U.S.C. 102(b) as being anticipated by products O1256 and O4378 of the 1993 Sigma Chemical Catalog.

In The 1993 Sigma Chemical Catalog product O1256 is a 4-mer oligonucleotide of poly dT nucleotides and product O4378 is a 4-mer oligonucleotide of poly dA nucleotides. It is noted that these oligonucleotides are fragments in length that are encompassed by the instantly claimed nucleic acids. They thus anticipate instant claims via segments therein which are poly T segments or poly A segments present in the SEQ ID NO: 7 (nucleic acid positions 169-171 and 81-84 respectively). Due to the claims 22-25 requiring only that **a** nucleic acid sequence share a percent identity with SEQ ID NO: 7, as few as 2 bp of the instant Sigma products that align 100% anticipate the claimed nucleic acids.

Objection to the claims

35. Claim 20 is objected to because of the following informalities: a typographical error in the spelling of diphosphate, "disphopate" line 2. Appropriate correction is required.

Conclusion

NEW GROUNDS FOR REJECTION AS NECESSITATED BY AMENDMENT

- Claims 10 and 20-25 are rejected under 35 U.S.C. § 101/112 – utility.
- Claims 20-25 are rejected under 35 U.S.C. 112, first paragraph – enablement.
- Claims 10 and 20-25 are rejected under 35 U.S.C. § 112, first paragraph – written description.
- Claims 22-25 are rejected as necessitated by amendment under 35 U.S.C. 112, second paragraph.
- Claims 20-25 are rejected under 35 U.S.C. 102(b) – GenBank accession number L37750
- Claims 20-25 are rejected under 35 U.S.C. 102(b) – products O1256 and O4378 of the 1993 Sigma Chemical Catalog.
- Claim 20 is objected.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The central **Fax number is (703) 872-9306**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Monika B. Sheinberg, whose telephone number is (571) 272-0749. The examiner can normally be reached on Monday-Friday from 9 A.M to 5 P.M. If attempts to reach the examiner by telephone are unsuccessful, the primary examiner in charge of the prosecution of this case, Jehanne Sitton, can be reached at (571) 272-0752. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst, Chantae Dessau, whose telephone number is (571) 272-0518, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

April 28, 2004
Monika B. Sheinberg
Art Unit 1634

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